Applicants have herein changed the numeric identifier <213> in each of the sequence listings SEQ ID Nos. 1-4 to read "not naturally occurring", thereby overcoming the Examiner's objection. Applicants attach hereto a corrected diskette containing the sequence listing.

The Examiner has requested that the specification be amended to reflect the SEQ ID Nos. (i.e., SEQ ID Nos. 1-4) in the sequence listing. Applicants have, hereinabove, amended the specification pages 41, 45-47, and 50 as requested by the Examiner.

The Examiner has requested that the elected species at page 43, Table A, be amended to include a hydrogen atom on the hydroxamide. Applicants have amended the specification accordingly.

II. CLAIM REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

The Examiner has rejected claims 60-61 under 35 U.S.C. § 112, first paragraph, on the grounds that the specification is not commensurate with the broad scope of the claims. Applicants respectfully traverse.

Applicants have submitted an enabling disclosure including the use of exemplified compounds that are believed to be the best mode, see pages 54-74, Examples 1-31, of the specification as originally filed. Applicants have also described multiple schemes of preparation and starting materials that could be used by one skilled in the art to prepare the claimed compounds, see pages 29-41, Schemes 1-4 and their descriptions, of the specification. Applicants have also described several biological assays, including human monocyte assay (page 44) and in vitro MMP-1 assay (page 45), which demonstrate the utility of the claimed compounds. Applicants have also provided a detailed description of methods for dosing and formulating the compounds of the invention, see pages 53-54.

Applicants traverse the Examiner's rejection on the grounds that the Examiner has failed to present a *prima facie* case that Applicants' specification is non-enabling because the Examiner has not provided any evidence that could question the results stated in Applicants' specification. An assertion by an Examiner that the enabling disclosure is not commensurate in scope with the protection sought must be supported by evidence of reasoning substantiating the doubts so expressed. In re Dinh-Nguyen et al., (C.C.P.A. 1974) 492 F2d 816, 181 U.S.P.Q. 46; In re Bowen, (C.C.P.A. 1974) 492 F2d 859, 181 U.S.P.Q. 48; and In re Armbruster (CCPA 1975) 512 F2d 676, 185 U.S.P.Q. 152. The Examiner has not provided any evidence with which to substantiate his doubts.

Applicants respectfully submit that small molecules, including hydroxamic acids, have been known in the MMP field to enable those skilled in the art to make and use the invention commensurate in scope with the claims. The courts have pointed out that "[n]ot every last detail [of an invention need] be described [in a patent specification], else patent specifications would turn into production specifications, which they were never intended to be." In re Gay, 309 F.2d 769, 774, 135

U.S.P.Q. 311, 316 (C.C.P.A. 1962). Citing the opinion in Gay, the Board of Patent Appeals and Interferences echoed this point in its statement that "the law does not require a specification to be a blueprint in order to satisfy the requirement for enablement under 35 U.S.C. 112, first paragraph," Staehelin v. Secher, 24 U.S.P.Q.2d 1513,1516 (Bd. Pat. App. & Int. 1992). Indeed, a specification need not describe - and best omits - that which is well-known in the art. See, e.g., In re Buchner, 929 F2d 660, 661, 18 U.S.P.Q.2d 1331, 1332 (Fed. Cir. 1991). The Examiner's attention is directed to the following patents, among many others, that are directed to small molecules that inhibit TACE:

U.S. Patent No. 6,326,516, entitled "Acetylenic beta-sulfonamido and phosphinic acid amide hydroxamic acid TACE inhibitors";

U.S. Patent No. 6,313,123, entitled "Acetylenic sulfonamide thiol TACE inhibitors";

U.S. Patent No. 6,288,086, entitled "N-hydroxy-2-(alkyl, aryl, or heteroaryl, sulfanyl, sulfinyl or sulfonyl)-3-substituted alkyl, aryl or heteroarylamides as matrix metalloproteinase inhibitors";

U.S. Patent No. 6,277,885, entitled "Acetylenic aryl sulfonamide and phosphinic acid amide hydroxamic acid TACE inhibitors";

U.S. Patent No. 6,228,869, entitled "Ortho-sulfonamido bicyclic hydroxamic acids as matrix metalloproteinase and TACE inhibitors";

U.S. Patent No. 6,225,311, entitled "Acetylenic alpha-amino acid-based sulfonamide hydroxamic acid TACE inhibitors";

U.S. Patent No. 6,200,996, entitled "Heteroaryl acetylenic sulfonamide and phosphinic acid amide hydroxamic acid TACE inhibitors";

U.S. Patent No. 6,197,795, entitled "Preparation and use of ortho-sulfonamido heteroaryl hydroxamic acids as matrix metalloproteinase and TACE inhibitors";

U.S. Patent No. 6,197,791, entitled "N-hydroxy-2-(alkyl, aryl, or heteroaryl, sulfanyl, sulfinyl or sulfonyl)-3-substituted alkyl, aryl or heteroarylamides as matrix metalloproteinase inhibitors";

U.S. Patent No. 6,180,403, entitled "Antisense inhibition of tumor necrosis factor alpha converting enzyme (TACE) expression";

U.S. Patent No. 6,172,057, entitled "N-Hydroxy-2-(alkyl, aryl, or heteroaryl sulfanyl, sulfinyl or sulfonyl)-3-substituted alkyl, aryl or heteroarylamides as matrix metalloproteinase inhibitors";

U.S. Patent No. 6,162,821, entitled "Preparation and use of ortho-sulfonamide heteroaryl hydroxamic acids as matrix metalloproteinase and TACE inhibitors";

U.S. Patent No. 6,162,814, entitled "Preparation and use of ortho-sulfonamido heteroaryl hydroxamic acids as matrix metalloproteinase and TACE inhibitors";

U.S. Patent No. 6,071,903, entitled "2,3,4,5-tetrahydro-1H-[1,4]-benzodiazepine-3-hydroxyamic acids";

U.S. Patent No. 6,013,466, entitled "TNF-alpha converting enzyme";

U.S. Patent No. 5,977,408, entitled "Preparation and use of beta-sulfonamido hydroxamic acids as matrix metalloproteinase and TACE inhibitors";

U.S. Patent No. 5,962,481, entitled "Preparation and use of ortho-sulfonamido heteroaryl hydroxamic acids as matrix metalloproteinase and TACE inhibitors";

U.S. Patent No. 5,929,097, entitled "Preparation and use of ortho-sulfonamido aryl hydroxamic acids as matrix metalloproteinase and TACE inhibitors";

U.S. Patent No. 5,830,742, entitled "TNF-alpha converting enzyme";

U.S. Patent No. 5,629,285, entitled "Inhibitors of TNF-alpha secretion"; and

U.S. Patent No. 5,594,106, entitled "Inhibitors of TNF-alpha secretion".

The Examiner's attention is also directed to other patents that are directed to both inhibitions of TACE and MMP, i.e.:

U.S. Patent No. 6,197,795, entitled "Preparation and use of ortho-sulfonamido heteroaryl hydroxamic acids as matrix metalloproteinase and TACE inhibitors";

U.S. Patent No. 6,162,821, entitled "Preparation and use of ortho-sulfonamide heteroaryl hydroxamic acids as matrix metalloproteinase and TACE inhibitors";

U.S. Patent No. 6,162,814, entitled "Preparation and use of ortho-sulfonamido heteroaryl hydroxamic acids as matrix metaloproteinase and TACE inhibitors";

U.S. Patent No. 5,977,408, entitled "Preparation and use of beta-sulfonamido hydroxamic acids as matrix metalloproteinase and TACE inhibitors";

U.S. Patent No. 5,962,481, entitled "Preparation and use of ortho-sulfonamido heteroaryl hydroxamic acids as matrix metalloproteinase and TACE inhibitors"; and

U.S. Patent No. 5,929,097, entitled "Preparation and use of ortho-sulfonamido aryl hydroxamic acids as matrix metalloproteinase and TACE inhibitors".

Applicants submit that the foregoing list is merely illustrative of the breadth of the art. Applicants further submit that the present specification needs not describe - and best omits - the numerous small molecules, including hydroxamic acids, TACE inhibitors that are well-known in the art. Therefore the claims are enabled.

Although Applicants submit that they are entitled to the claims as originally filed, in the interest of expediting prosecution, Applicants have, hereinabove, amended claims 60-61. Specifically, Applicants have amended the claims in light of the Examiner's rejection to recite: "at least 100 fold IC_{50} selectivity for TACE over MMP-1 wherein MMP-1 activity is determined by an MMP-1 in vitro assay and wherein TACE activity is determined by a human monocyte assay". Support for this amendment can be found throughout the specification, *inter alia*, page 24, lines 24-29, and page 52, lines 8-12. Applicants reiterate that the claims as amended are not to be construed as an admission that the Examiner's position on 35 U.S.C. § 112 has merit. The amendment is merely directed at one embodiment of the invention that is free of allegations raised by the Examiner. Applicants submit that they reserve and intend to file a divisional application directed to the contested matter.

The Examiner has cited Amour or Andrew as references that are not prior art (see Office Action, pages 4 and 5). Applicants respectfully submit that neither Amour nor Andrew teaches that the presently claimed method is inoperative for the recited selectivity for TACE. The Examiner relies on page 42, Table 1, of Amour that describes BB-94 as being 2.8 fold more selective for TACE over MMP-1. The Examiner also relies on page 153, table 3, of Andrew. The Examiner states that "compounds 7 and 8 appear to exhibit high selectivity for TACE over MMP-1 (collagenase-1), TACE gets "+" and MMP gets "+++", where these mean Ki <1nM and 500 nM-1μM respectively suggesting at least 500 fold selectivity." The Examiner further states "Several other compounds exhibited intermediate selectivity "++" or 100-500 nM for Ki, corresponding to 100-500 fold selectivity." The Examiner concludes that based on these references (which are not prior art as acknowledged by the Examiner) selectivity for TACE over MMP-1 is difficult to obtain and not very predictable for those skilled in the art. Applicants respectfully traverse the Examiner's position.

The Amour or the Andrew references do not demonstrate that the claimed features are non-enabled. Neither references state that any of the compounds have >100 fold selectivities. Andrew recites broad categories for selecticity of hydroxamate-based TACE inhibitors. However Andrew states no specific selectivities IC50 data. Applicants respectfully submit that on page 153, table 3, of Andrew, "+" means Ki <100 nM, rather that <1 nM as stated above by the Examiner. Since no specific data are reported, under the teaching of Andrew, examples 7 and 8 of Andrew can have as little as 5 fold selectivity. On the contrary, Applicants respectfully submit that, as stated above, the specification provides several assays for screening the compounds of the invention, see page 38 (in vitro TACE assay) and page 42 (Inhibition of Human Collagenase (MMP-1)). Applicants have even provided, in the specification as filed, specific IC50 data for preferred compounds of the invention showing the claimed selectivities for TACE. The Examiner has not presented any reasons why the implementation of the assays and the screening of the genus would present any difficulty to the skilled artisan. Applicants respectfully submit that there is no difficulty, and the claims are enabled. Thus, Applicants respectfully submit that based on the above arguments and the amendments to claims 60-61, the Examiner has failed to present a prima facie case for non-enablement.

III. New Claims 80-81

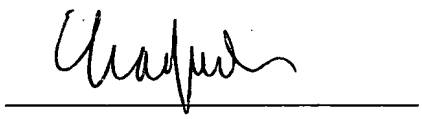
Applicants have, hereinabove, added new claims 80-81 directed to a method of inhibiting the cleavage of TNF-α from cell membranes without inhibiting MMP-1 by administering a small molecule (claim 80) or a hydroxamic acid compound (claim 81) that possesses at least 500 fold IC_{50} selectivity for TACE over MMP-1. Support for new claims 80-81 can be found throughout the specification as filed, *inter alia*, on page 24, lines 24-29. The new claims add no new matter.

IV. Conclusions

Based on the above arguments, amendments to claims 60-61, and the legal precedents, Applicants respectfully request that the Examiner remove his non-enablement rejection and allow claims 60-61 and 80-81 to issue.

Date: December 11'01

Respectfully submitted,



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